PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 471/04, A61K 31/435
// (C07D 471/04, 231:00, 221:00)

A1

(11) International Publication Number: **WO 94/03453**

(43) International Publication Date: 17 February 1994 (17.02.94)

(21) International Application Number: PCT/GB93/01635

(22) International Filing Date: 3 August 1993 (03.08.93)

(30) Priority data:
9216783.2 7 August 1992 (07.08.92) GB

(71) Applicant *(for all designated States except US):* ZENECA LIMITED [GB/GB]; Imperial Chemical House, 9 Millbank, London SW1P 3JF (GB).

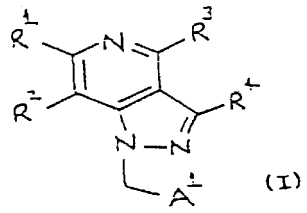
(72) Inventors; and
(75) Inventors/Applicants *(for US only) :* RATCLIFFE, Arnold, Harry [GB/GB]; 63 Dickens Lane, Poynton, Cheshire SK10 1NN (GB). MASEK, Brian, Bernard [US/US]; 224 West Evergreen Street, West Grove, PA 19390 (US).

(74) Agent: SMITH, Stephen, Collyer; ICI Group Patents Services Department, P.O. Box 6, Shire Park, Welwyn Garden City, Hertfordshire AL7 1HD (GB).

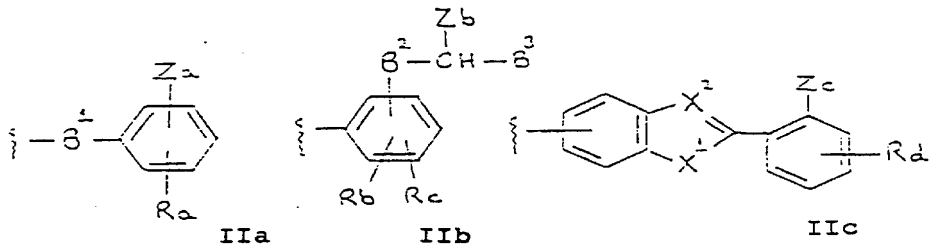
(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PYRAZOLOPYRIDINE DERIVATIVES AS ANGIOTENSIN II ANTAGONISTS



(I)



IIa IIb IIc

(57) Abstract

Compounds of formula (I) wherein A^1 is a group of partial formula IIa, IIb or IIc, Za and Zb are 1H-tetrazol-5-yl, a carboxy group or in vivo hydrolysable ester thereof, -CO.NH.(1H-tetrazol-5-yl), or a group of the formula -CO.NH.CO_2R^8 and Zc is 1H-tetrazol-5-yl, carboxy or in vivo hydrolysable ester thereof or a group of the formula CF_3SO_2NH-. The novel compounds are of value in treating conditions such as hypertension and congestive heart failure.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**FR**	France	**MR**	Mauritania
AU	Australia	**GA**	Gabon	**MW**	Malawi
BB	Barbados	**GB**	United Kingdom	**NE**	Niger
BE	Belgium	**GN**	Guinea	**NL**	Netherlands
BF	Burkina Faso	**GR**	Greece	**NO**	Norway
BG	Bulgaria	**HU**	Hungary	**NZ**	New Zealand
BJ	Benin	**IE**	Ireland	**PL**	Poland
BR	Brazil	**IT**	Italy	**PT**	Portugal
BY	Belarus	**JP**	Japan	**RO**	Romania
CA	Canada	**KP**	Democratic People's Republic of Korea	**RU**	Russian Federation
CF	Central African Republic			**SD**	Sudan
CG	Congo	**KR**	Republic of Korea	**SE**	Sweden
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovak Republic
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LU**	Luxembourg	**TD**	Chad
CS	Czechoslovakia	**LV**	Latvia	**TG**	Togo
CZ	Czech Republic	**MC**	Monaco	**UA**	Ukraine
DE	Germany	**MG**	Madagascar	**US**	United States of America
DK	Denmark	**ML**	Mali	**UZ**	Uzbekistan
ES	Spain	**MN**	Mongolia	**VN**	Viet Nam
FI	Finland				

Pyrazolopyridine derivatives as Angiotensin II antagonists

This invention concerns novel heterocyclic derivatives and, more particularly, novel pyrazolopyridine derivatives which possess pharmacologically useful properties in antagonising at least in part one or more of the actions of the substances known as angiotensins, and in particular of that known as angiotensin II (hereinafter referred to as "AII"). The invention also concerns pharmaceutical compositions of the novel compounds for use in treating diseases or medical conditions such as hypertension, congestive heart failure and/or hyperaldosteronism in warm-blooded animals (including man), as well as in other diseases or medical conditions in which the renin-angiotensin-aldosterone system plays a significant causative role. The invention also includes processes for the manufacture of the novel compounds and their use in treating one of the afore-mentioned diseases or medical conditions and for the production of novel pharmaceuticals for use in such medical treatments.

The angiotensins are key mediators of the renin-angiotensin-aldosterone system, which is involved in the control of homeostasis and fluid/electrolyte balance in many warm-blooded animals, including man. The angiotensin known as AII is produced by the action of angiotensin converting enzyme (ACE) on angiotensin I, itself produced by the action of the enzyme renin on the blood plasma protein angiotensinogen. AII is a potent spasmogen especially in the vasculature and is known to increase vascular resistance and blood pressure. In addition, the angiotensins are known to stimulate the release of aldosterone and hence result in vascular congestion and hypertension via sodium and fluid retention mechanisms. Hitherto there have been a number of different approaches to pharmacological intervention in the renin-angiotensin-aldosterone system for therapeutic control of blood pressure and/or fluid/electrolyte balance, including, for example, inhibiting the actions of renin or ACE. However, there remains a continuing need for an alternative approach because of the side-effects and/or idiosyncratic reactions associated with any particular therapeutic approach.

Certain imidazopyridines and pyrrolopyridines having AII antagonist activity are described in European Patent Application,

Publication Nos. 399731 and 497516 respectively.

We have now discovered that the compounds of the invention (set out below) surprisingly antagonise one or more of the actions of the substances known as angiotensins (and in particular of AII) and thus minimise the physiological effects associated with their presence in warm-blooded animals (including man) and this is the basis of the invention.

According to the invention there is provided a pyrazolopyridine derivative of the formula I (set out hereinafter, together with the other chemical formulae identified by Roman numerals) wherein R^1 is hydrogen, (1-8C)alkyl, (3-8C)cycloalkyl, phenyl or substituted (1-4C)alkyl, the latter containing one or more fluoro substituents or bearing a (3-8C)cycloalkyl, (1-4C)alkoxy or phenyl substituent; R^2 is hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, carboxy, (1-4C)alkoxycarbonyl, (3-6C)alkenyloxycarbonyl, cyano, nitro, carbamoyl, (1-4C)alkanoyl, N-alkylcarbamoyl and di-(N-alkyl)carbamoyl of up to 7 carbon atoms, amino, alkylamino and dialkylamino of up to 6 carbon atoms, 3-(1-4C)alkylureido and (1-4C)alkanoylamino; R^3 is selected from halogeno, (1-4C)alkoxy, hydroxy, amino, alkylamino and dialkylamino of up to 6 carbon atoms, and any of the values defined for R^1; R^4 is selected from (1-4C)alkoxy, halogeno, hydroxy(1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, (3-6C)alkenyloxycarbonyl, cyano, nitro, carbamoyl, N-alkylcarbamoyl and di-(N-alkyl)carbamoyl of up to 7 carbon atoms, (1-4C)alkanoyl, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl, pyridyl and any of the values defined for R^1;

A^1 is a group of the partial formula IIa, IIb or IIc wherein (1) in partial formula IIa, B^1 is a direct bond or is phenylene optionally bearing a substituent selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, (1-4C)alkanoyl, trifluoromethyl, cyano and nitro; Ra is hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano, trifluoromethyl or nitro; and Za is 1H-tetrazol-5-yl, a carboxy group or in vivo hydrolysable ester thereof, -CO.NH.(1H-tetrazol-5-yl), or a group of the formula $-CO.NH.CO_2R^8$ in which R^8 is (1-6C)alkyl,

(3-8C)cycloalkyl, trifluoromethyl or phenyl;
(2) in partial formula IIb, B^2 is oxygen, sulphur or a group of the formula $-NR^5-$ in which R^5 is hydrogen or (1-4C)alkyl; Zb has any of the values defined above for Za; B^3 is phenyl optionally bearing one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy and halogeno; and Rb and Rc are independently selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy and halogeno; and
(3) in partial formula IIc, Zc is 1H-tetrazol-5-yl, carboxy or in vivo hydrolysable ester thereof or a group of the formula CF_3SO_2NH-; Rd is selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, cyano and nitro; X^1 is oxygen, sulphur or a group of the formula $-NR^6-$ in which R^6 is hydrogen or (1-4C)alkyl; and X^2 is nitrogen or is a group of the formula $-C(R^7)=$ wherein R^7 is hydrogen, (1-4C)alkyl optionally containing one or more fluoro substituents, carbamoyl or N-alkyl or di-(N-alkyl)carbamoyl of up to 7 carbon atoms, halogeno, cyano, (1-4C)alkoxycarbonyl or (1-4C)alkanoyl;

and wherein any of said phenyl moieties may be unsubstituted or bear one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano and trifluoromethyl; or an N-oxide thereof; or a non-toxic salt thereof.

It will appreciated that, depending on the nature of the substituents, certain of the formula I compounds may possess one or more chiral centres and may be isolated in one or more racemic or optically active forms. It is to be understood that this invention concerns any form of such a compound of formula I which possesses the afore-mentioned useful pharmacological properties, it being well known how to make optically active forms, for example by synthesis from suitable chiral intermediates, and how to determine their pharmacological properties, for example by use of the standard tests described hereinafter.

It is to be understood that generic terms such as "alkyl" include both straight and branched chain variants when the carbon numbers permit. However, when a particular radical such as "propyl" is given, it is specific to the straight chain variant, branched chain variants such as "isopropyl" being specifically named where intended.

The same convention applies to other radicals.

Particular values for R^1, R^3 or R^4 include, by way of example, for alkyl: methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, pentyl and hexyl; for cycloalkyl: cyclopropyl, cyclopentyl and cyclohexyl; for alkyl bearing one or more fluoro substitutents: fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl and pentafluoroethyl; and for alkyl bearing a cycloalkyl, (1-4C)alkoxy or phenyl substituent: cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-methoxyethyl, 2-ethoxyethyl, benzyl, 1-phenylethyl and 2-phenylethyl.

Particular values for R^2, R^3 or R^4, when it is halogeno is, for example, fluoro, chloro, bromo or iodo; and when it is alkoxy is, for example, methoxy or ethoxy;

Particular values for R^2 or R^4 include, by way of example, for alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl; for alkenyloxycarbonyl: allyloxycarbonyl, 2-methyl-2-propenyloxycarbonyl and 3-methyl-3-butenyloxycarbonyl; for alkanoyl: formyl, acetyl and propionyl; for N-alkylcarbamoyl: N-methyl and N-ethylcarbamoyl; and for di(N-alkyl)carbamoyl: N,N-dimethylcarbamoyl and N,N-diethylcarbamoyl;

Particular values for R^2 or R^3 are, by way of example, for alkylamino: methylamino, ethylamino or butylamino; and for dialkylamino: dimethylamino, diethylamino or dipropylamino.

Particular values for R^2 include, by way of example, for alkanoylamino: formamido, acetamido and propanamido; and for 3-alkylureido: 3-methylureido, 3-ethylureido and 3-propylureido.

Particular values for R^4 include, by way of example, for hydroxyalkyl: hydroxymethyl, 1-hydroxyethyl and 2-hydroxyethyl; for alkylthio: methylthio and ethylthio; for alkylsulphinyl: methylsulphinyl and ethylsulphinyl; and for alkylsulphonyl: methylsulphonyl and ethylsulphonyl;

A particular value for R^2, R^5 or R^6 when it is alkyl is, for example, methyl, ethyl or propyl.

A particular value for Ra, Rb, Rc, Rd or an optional substituent on B^1 when it is phenylene, or an optional substituent or substituents on B^3, when it is alkyl is, for example, methyl or ethyl;

when it is alkoxy is, for example, methoxy or ethoxy; and when it is halogeno is, for example, fluoro, chloro or bromo.

A particular value for an alkanoyl substituent on B^1 when it is phenylene is, for example, formyl, acetyl or propionyl.

A particular value for Za, Zb, or Zc when it is an in vivo hydrolysable ester is, for example an ester derived from a (1-6C)alkanol such as methanol or ethanol, or phenol, glycerol or the like.

A particular value for R^8 when it is alkyl is, for example, methyl, ethyl, propyl, isopropyl, butyl or pentyl; and when it is cycloalkyl is, for example, cyclobutyl, cyclopentyl or cyclohexyl.

A particular value for R^7 includes, by way of example,
for alkyl: methyl and ethyl;
for alkyl containing one or more fluoro substitutents: fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl and pentafluoroethyl;
for N-alkylcarbamoyl: N-methyl and N-ethylcarbamoyl;
for di(N-alkyl)carbamoyl: N,N-dimethylcarbamoyl and N,N-diethylcarbamoyl;
for halogeno: fluoro, chloro, bromo or iodo;
for alkoxycarbonyl: methoxycarbonyl or ethoxycarbonyl; and
for alkanoyl: formyl, acetyl or propionyl.

Particular values for optional substituents which may be present on phenyl moieties include, by way of example, for halogeno: fluoro, chloro and bromo; for alkyl: methyl and ethyl; and for alkoxy: methoxy and ethoxy.

A preferred value for R^1 or R^3 is, for example, (1-4C)alkyl such as methyl or ethyl.

A preferred value for R^2 is, for example, hydrogen.

A preferred value for R^4 is, for example, phenyl.

A preferred value for A^1 is, for example, a group of partial formula IIa.

A preferred value for B^1 is, for example, a p-phenylene group.

A preferred value for Za, Zb or Zc is, for example, carboxy or 1H-tetrazol-5-yl.

An especially preferred value for Za is when it is attached at the ortho position relative to B^1. Za is 1H-tetrazol-5-yl is

particularly preferred.

A preferred value for B^2 is, for example, oxygen.

A preferred value for X^1 is, for example, oxygen, and for X^2 is, for example, nitrogen or $-C(R^7)=$ in which R^7 is hydrogen or halogeno.

A particularly preferred combination of values is, for example, when R^1 and R^3 are both alkyl.

Particular groups of compounds of the invention include, for example,

(1) Compounds of the formula I wherein A^1 is a group of partial formula IIa in which Za is tetrazolyl or carboxy attached ortho to B^1, and R^1-R^4, B^1 and Ra have any of the meanings defined above;

(2) Compounds of the formula I wherein A^1 is a group of partial formula IIb in which B^2 is oxygen and is attached para to the pyrazolopyridine moiety, Zb is tetrazolyl or carboxy, and R^1-R^4, Rb, Rc and B^3 have any of the meanings defined above;

(3) Compounds of the formula I wherein A^1 is a group of partial formula IIc in which X^1 is oxygen or NH, X^2 is $-C(R^7)=$, R^7 is hydrogen or halogeno, Zc is tetrazolyl or carboxy, R^1-R^4 and Rd have any of the meanings defined above, and the pyrazolopyridine ring is attached para to X^1; and

(4) Compounds of the formula I wherein A^1 is a group of partial formula IIc in which X^1 is oxygen or sulphur, X^2 is nitrogen, Zc is tetrazolyl or carboxy, R^1-R^4 and Rd have any of the meanings defined above, and the pyrazolopyridine ring is attached para to X^1.

A preferred group of compounds of the formula I comprises those compounds of the formula Ia wherein R^1, R^2, R^3 and R^4 have any of the meanings defined above; R^9 and R^{10} are independently selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, cyano and nitro; and Z^1 is 1H-tetrazol-5-yl or carboxy; and the non-toxic salts thereof.

A preferred sub-group of compounds of the formula Ia comprises those compounds in which R^1 is (1-4C)alkyl; R^2, R^9 and R^{10} are all hydrogen; R^3 is (1-4C)alkyl; R^4 is phenyl optionally bearing a halogeno, (1-4C)alkoxy or (1-4C)alkyl substituent; and the non-toxic salts thereof.

Compounds of the invention which are of particular interest include, for example, the specific embodiments set out hereinafter in the accompanying Examples and these are provided as a further feature of the invention.

Although all of the formula I compounds can form salts with suitable acids, it will be appreciated that those compounds of formula I wherein Za, Zb or Zc is other than an ester group or in which R^2 or R^4 bear a carboxy group can form salts with bases as well as with acids. Particularly suitable non-toxic salts for such compounds therefore also include, for example, salts with bases affording physiologically acceptable cations, for example, alkali metal (such as sodium and potassium), alkaline earth metal (such as magnesium and calcium), aluminium and ammonium salts, as well as salts with suitable organic bases, such as with ethanolamine, methylamine, diethylamine or triethylamine, as well as salts with acids forming physiologically acceptable anions, such as salts with mineral acids, for example with hydrogen halides (such as hydrogen chloride and hydrogen bromide), sulphuric and phosphoric acid, and with strong organic acids, for example with p-toluenesulphonic and methanesulphonic acids.

The compounds of formula I may be obtained by standard procedures of organic chemistry well known in the art for the production of structurally analogous compounds. Such procedures are provided as a further feature of the invention and include, by way of example, the following procedures in which the generic radicals have any of the values given above, unless stated otherwise:

a) For those compounds in which A^1 is a group of partial formula IIa, IIb or IIc in which Za, Zb and Zc respectively are carboxy, a carboxylic acid derivative of the formula IIIa, IIIb or IIIc in which Qa, Qb and Qc respectively are protected carboxy groups selected from (1-6C)alkoxycarbonyl (especially methoxy-, ethoxy-, propoxy- or t-butoxy-carbonyl), phenoxycarbonyl, benzyloxycarbonyl and carbamoyl, is converted to carboxy.

The conversion may be carried out, for example by hydrolysis, conveniently in the presence of a suitable base such as an

alkali metal hydroxide, for example, lithium, sodium or potassium hydroxide. The hydrolysis is generally carried out in the presence of a suitable aqueous solvent or diluent, for example in an aqueous (1-4C)alkanol, such as aqueous methanol or ethanol. However, it may also be performed in a mixture of an aqueous and non-aqueous solvent such as water and toluene using a conventional quaternary ammonium phase transfer catalyst. The hydrolysis is generally performed at a temperature in the range, for example, 0 - 120°C, depending on the reactivity of the group Q. In general, when Q is carbamoyl, temperatures in the range, for example, 40 - 120°C are required to effect the hydrolysis.

Alternatively, when Qa, Qb or Qc is benzyloxycarbonyl the conversion may also be performed by hydrogenolysis, for example using hydrogen at 1-3 bar in the presence of a suitable catalyst, such as palladium on charcoal or on calcium sulphate, in a suitable solvent or diluent such as a (1-4C)alkanol (typically ethanol or 2-propanol) and at a temperature in the range, for example, 0 - 40°C.

Further, when Qa, Qb or Qc is t-butoxycarbonyl, the conversion may also be carried out by hydrolysis at a temperature in the range, for example, 0 - 100°C, in the presence of a strong acid catalyst, such as trifluoroacetic acid. The hydrolysis may either be performed in an excess of the acid or in the presence of a suitable diluent such as tetrahydrofuran, t-butyl methyl ether or 1,2-dimethoxyethane.

b) For those compounds of formula I in which A^1 is a group of the partial formula IIa, IIb or IIc in which Za, Zb and Zc respectively are tetrazolyl, a compound of the formula IVa, IVb or IVc in which La, Lb and Lc respectively are suitable protecting group, such as trityl, benzhydryl, trialkyltin (for example trimethyltin or tributyltin) or triphenyltin, affixed to a nitrogen of the tetrazolyl moiety, is deprotected.

The reaction conditions used to carry out the deprotection necessarily depend on the nature of the group La, Lb or Lc. As an illustration, when it is trityl, benzhydryl, trialkyltin or triphenyltin, the decomposition conditions include, for example, acid catalysed hydrolysis in a mineral acid (such as aqueous hydrochloric

acid), conveniently in an aqueous solvent (such as aqueous dioxan or 2-propanol). Alternatively, a trityl or benzhydryl group may be removed by hydrogenolysis, for example as described in (a) above for conversion of a benzyloxycarbonyl to a carboxy.

Compounds of the formula IVa, IVb or IVc wherein La, Lb and Lc respectively are trialkyltin or triphenyltin may be obtained, for example, by reaction of a nitrile of the formula VIIIa, VIIIb or VIIIc with a trialkyltin azide, such as tributyltin azide, or triphenyltin azide respectively. The reaction is conveniently carried out in a suitable solvent or diluent, such as toluene or xylene, and at a temperature in the range, for example, 50-150°C. In a modified procedure, the tetrazolyl group may be generated directly by in situ removal of the trialkyltin or triphenyltin group without prior isolation of the intermediate, for example by the addition of aqueous mineral acid or gaseous hydrogen chloride to the reaction mixture. The nitriles of the formula VIIIa, VIIIb or VIIIc may be obtained, for example, by alkylation of a compound of the formula V with a nitrile of the formula IXa, IXb or IXc respectively wherein Hal. stands for a suitable leaving group such as chloro, bromo, iodo, methanesulphonyloxy or p-toluenesulphonyloxy, using similar conditions to those used in process (c) described hereinafter. The necessary compounds of formula IXa, IXb or IXc, as well as those of formula VIa, VIb, VIc, VIIa, VIIb or VIIc described herein, may be obtained, for example, as described in European patent application, publication nos. 253310, 291969, 453210, 434249, 430709 and International patent application no. WO 91/11999. Trialkyltin azides and triphenyltin azides are either commercially available or may be prepared by standard procedures well known in the art, such as by reaction of a trialkyltin halide with an alkali metal azide.

c) A compound of the formula V is alkylated with a compound of the formula VIa, VIb or VIc wherein Hal. stands for a suitable leaving group such as chloro, bromo, iodo, methanesulphonyloxy or p-toluenesulphonyloxy.

The reaction is generally carried out in the presence of a suitable base, for example, an alkali metal alkoxide such as sodium methoxide or sodium ethoxide or an alkali metal hydride such as sodium

hydride or an alkali metal carbonate such as sodium or potassium carbonate, or an organic base such as diisopropylethylamine and in a suitable solvent or diluent, for example, a (1-4C)alkanol such as methanol or ethanol when an alkali metal alkoxide is used, or in a polar solvent such as N,N-dimethylformamide or N-methylpyrrolidone and at a temperature in the range, for example, 10 - 100°C. Alternatively, a quaternary ammonium hydroxide may be used in a mixture of an aqueous and non-aqueous solvent such as water and dichloromethane. In carrying out process (c), when in the starting material Za, Zb or Zc is an acidic group, about two molecular equivalents of a suitable base is generally required, whereas when Za, Zb or Zc is a non-acidic group the presence of one molecular equivalent of a suitable base is generally sufficient.

Procedure (c) is particularly suitable for the production of those compounds of the formula I in which Za, Zb or Zc is an ester group for example wherein Za, Zb or Zc is an (1-6C)alkyl, benzyl or phenyl ester, which compounds are also starting materials of formula IIIa, IIIb and IIIc respectively for the reaction described in (a) above. Similarly, using an analogous procedure, but starting with the appropriate halomethyl tetrazolyl derivative of the formula VIIa, VIIb or VIIc, the starting materials of the formula IVa, IVb or IVc respectively may be obtained for procedure (b).

Certain of the compounds of formula V are already known and the remainder can be made by analogy therewith using standard procedures of organic chemistry well known in the art, for example as described in standard works of heterocyclic chemistry such as that edited by Elderfield or "Chemistry of Heterocyclic Compounds" edited by Weissberger, or as illustrated in Scheme 1 from a suitably substituted 4-pyridone or 4-halopyridine. It will be appreciated that many compounds of the formula V may be obtained from other compounds of the formula V by routine funtional group modification, for example, by nucleophilic displacement of R^4 when it is halogeno using an alkali metal alkoxide, alkanethiolate or cyanide under standard conditions. Suitably substituted 4-pyridones may be obtained, for example, as described in European patent application, publication nos. 453210 and 499416 or by analogy therewith.

(d) For those compounds of formula I wherein A^1 is a group of partial structure IIc in which Zc is a group of the formula CF_3SO_2NH-, a compound of formula X is reacted with trifluoromethanesulphonic acid anhydride.

The reaction is preferably carried out in the presence of a base, such as triethylamine, and conveniently in a suitable solvent or diluent, for example dichloromethane, and at a temperature in the range of -78°C to ambient temperature. The compounds of the formula X may be obtained by alkylation of a compound of formula V with a compound of the formula XI (itself obtained using analogous procedures to those described in EPA 429257 and 430709) using similar conditions to those of process (c) above, followed by reduction of the nitro group in the intermediate obtained, for example by conventional catalytic hydrogenation.

Whereafter, those compounds of formula I wherein Za, Zb or Zc is 1H-tetrazol-5-yl may be obtained by stepwise conversion of a compound of the formula I wherein Za, Zb or Zc is a carboxylic acid or ester group respectively into the corresponding nitrile under standard conditions, followed by reaction of the nitrile with an azide such as an alkali metal azide, preferably in the presence of an ammonium halide, and preferably in the presence of a suitable polar solvent such as N,N-dimethylformamide and at a temperature in the range, for example, 50 to 160°C.

Whereafter, those compounds of the formula I wherein Za, Zb or Zc is -CO.NH.(1H-tetrazol-5-yl), a group of the formula $-CO.NH.SO_2R^8$ or an ester group, may be obtained, for example, by reacting a corresponding carboxylic acid of the formula I in which Za, Zb or Zc is carboxy (or a reactive derivative of said acid) with 5-aminotetrazole, a sulphonamide of the formula $NH_2.SO_2R^8$ or a salt thereof (for example, an alkali metal salt), or an appropriate alcohol or with a salt thereof (for example, an alkali metal salt thereof). Suitable reactive derivatives include, for example the chloride, bromide, azide, anhydride and mixed anhydride with formic or acetic acid of the carboxylic acid of formula I as defined above. When the free acid form is used, the reaction is generally carried out in the presence of a suitable dehydrating agent such as

dicyclohexycarbodiimide or 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide in the presence of a base such as triethylamine, pyridine or 4-dimethylaminopyridine. When a reactive derivative is used, either the reaction is carried out in the presence of a base such as mentioned above, or, for the preparation of a compound of the formula I wherein Za, Zb or Zc is a group of the formula $-CO.NH.SO_2R^8$ or an ester group, the sulphonamide or hydroxy compound is used in the form of a salt, such as its alkali metal salt (in particular the lithium, sodium or potassium salt thereof). The reaction is generally performed in the presence of a suitable diluent or solvent such as dioxan, t-butyl methyl ether or tetrahydrofuran and at a temperature in the range, for example, 0 - 60°C.

Whereafter, when an N-oxide derivative of a compound of the formula I is required, a compound of the formula I is oxidised. Suitable oxidising agents include those well known in the art for the conversion of nitrogen heterocycles to their corresponding N-oxide derivatives, for example, hydrogen peroxide or an organic peracid such as m-chloroperbenzoic acid or peracetic acid. The oxidation is preferrably carried out in a suitable conventional solvent or diluent for such oxidations, for example dichloromethane, chloroform or acetic acid, and at a temperature in the general range, for example 0 to 80°C.

Whereafter, when a non-toxic salt of a compound of formula I is required, it may be obtained, for example, by reaction with the appropriate base affording a physiologically acceptable cation, or with the appropriate acid affording a physiologically acceptable anion, or by any other conventional salt formation procedure.

Further, when an optically active form of a compound of formula I is required, one of the aforesaid processes may be carried out using an optically active starting material. Alternatively, the racemic form of a compound of formula I in which Za, Zb or Zc is an acidic group may be resolved, for example by reaction with an optically active form of a suitable organic base, for example, ephedrine, N,N,N-trimethyl(1-phenylethyl)ammonium hydroxide or 1-phenylethylamine, followed by conventional separation of the diastereoisomeric mixture of salts thus obtained, for example by fractional crystallisation from a suitable solvent, for example a

(1-4C)alkanol, whereafter the optically active form of said compound of formula I may be liberated by treatment with acid using a conventional procedure, for example using an aqueous mineral acid such as dilute hydrochloric acid.

According to a further aspect of the invention, there is provided a process for the manufacture of a compound of the formula I wherein A^1 is a group of partial structure IIa in which Za is tetrazolyl, B^1 is p-phenylene optionally bearing a substituent selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, (1-4C)alkanoyl, trifluoromethyl, cyano and nitro, and R^1, R^2, R^3, R^4 and Ra, have any of the meanings defined hereinbefore; which comprises reaction of a compound of the formula XII wherein P^1 is an electron-deficient phenyl group; Re is hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, (1-4C)alkanoyl, trifluoromethyl, cyano or nitro; and R^1, R^2, R^3, R^4 and Ra have any of the values defined above with a base selected from an alkali metal hydroxide, (1-12C)alkanolate, (1-12C)alkanethiolate, phenolate, thiophenolate or diphenylphosphide, wherein any phenyl ring of the latter three groups may optionally bear a (1-4C)alkyl, (1-4C)alkoxy or halogeno group.

A particular value for P^1 includes, for example, a phenyl group bearing 1, 2 or 3 electron-withdrawing groups independently selected from nitro, cyano and trifluoromethyl.

A particular value for Re when it is alkyl is, for example, methyl or ethyl; when it is alkoxy is, for example, methoxy or ethoxy; when it is alkanoyl is, for example, formyl, acetyl or propionyl; and when it is halogeno is, for example, fluoro, chloro, bromo or iodo.

A particular value for a base includes the following by way of example:-

for an alkali metal hydroxide: sodium or potassium hydroxide;

for an alkali metal alkanolate: an alkali metal (1-8C)alkanolate, for example an alkali metal (1-4C)alkoxide, such as sodium or potassium methoxide, ethoxide, propoxide or butoxide;

for an alkali metal alkanethiolate: an alkali metal (1-8C)alkanethiolate, for example an alkali metal (1-4C)alkanethiolate such as sodium or potassium methanethiolate, ethanethiolate,

propanethiolate or butanethiolate.

A particular value for an optional substituent on a phenyl group of an alkali metal phenolate, thiophenolate or diphenylphosphide, when it is alkyl is, for example, methyl or ethyl; when it is alkoxy is, for example, methoxy or ethoxy; and when it is halogeno is, for example, fluoro, chloro or bromo.

A preferred value for P^1 is, for example, a nitrophenyl group, especially 4-nitrophenyl.

A particularly preferred base is an alkali metal alkanethiolate such as sodium or potassium propanethiolate, an alkali metal alkanolate such as sodium or potassium ethoxide or methoxide, or an alkali metal thiophenolate such as sodium or potassium 4-fluorothiophenolate.

It will be appreciated that when the base is an alkali metal alkanolate, alkanethiolate, phenolate, thiophenolate or diphenylphosphide, it may be generated in situ from the corresponding alkanol, alkanethiol, phenol, thiophenol or diphenylphosphine with a suitable alkali metal base such as an alkali metal hydride, for example, lithium, potassium or sodium hydride.

The process of the invention is particularly useful for the preparation of compounds of the formula I wherein the tetrazolyl group is at the ortho position relative to the adjacent phenyl group.

The reaction is conveniently carried out in a suitable inert organic solvent or diluent, for example, a polar solvent such as N,N-dimethylformamide or N-methylpyrrolidone. Alternatively, an alkanol such as methanol or ethanol may be used, for example, when an alkali metal hydroxide or alkoxide such as sodium or potassium hydroxide, methoxide or ethoxide is employed. The reaction is generally carried out at a temperature in the range, for example, -30°C to 50°C. It will be appreciated that the choice of temperature will depend on the nature of the base employed. For example, when an alkali metal alkanethiolate or alkanolate is used, a temperature in the range of 0°C to ambient temperature is preferred.

Compounds of the formula XII may be obtained by reaction of a boronic acid of the formula XIII with a compound of the formula XIV wherein P^1 is an electron-deficient phenyl group having any of the meanings defined above and W is a bromo, iodo or trifluoromethane-

sulphonyloxy group, in the presence of a palladium(0) or palladium(II) catalyst, such as tetrakis(triphenylphosphine)palladium(0) or palladium (II) chloride. The reaction is preferably carried out in the presence of a base, such as sodium or potassium carbonate, in an inert solvent or diluent, for example, a hydrocarbon such as toluene or xylene, an ether, such as dioxan or tetrahydrofuran, an (1-4C)alkanol such as methanol or ethanol, water, or mixture thereof, for example a mixture of water, methanol and toluene, and at a temperature in the range of, for example, 50°C to 150°C., and conveniently at or about the reflux temperature of the solvent or mixture of solvents used.

Compounds of the formula XIII may be obtained, for example, by heating at reflux a 4-methylphenylboronic acid in a solvent such as methyl chloroform with azeotropic removal of water, followed by radical bromination of the product which may be carried out in situ, for example with bromine or N-bromosuccinimide in the presence of azo(bisisobutyronitrile). The resultant 4-bromomethylphenylboronic acid anhydride may then be used to alkylate a compound of the formula V (using similar alkylation conditions to those used in process (c) described above), followed by subsequent acidic hydrolysis, to give a formula XIII compound. Alternatively the product from the alkylation step prior to hydrolysis may be isolated and reacted directly with a compound of the formula XIV under similar conditions to those described above to obtain a formula XII compound directly. In a yet further alternative procedure, a 4-methylphenylboronic acid and an appropriate alkanediol, for example 2,2-dimethylpropan-1,3-diol, may be heated at reflux in a solvent (such as cyclohexane) with azeotropic removal of water followed by free radical bromination of the product, which may be carried out in situ. The resultant bromomethyl compound may then be reacted using analogous procedures to those described above for the 4-bromomethylphenylboronic acid anhydride to obtain a formula XIII compound or a compound of the formula XII directly. Compounds of the formula XIV may be obtained, for example, by reaction of an appropriately substituted benzoyl chloride with a amine of formula $P^1.NH_2$ under standard conditions. The resultant amide is then, for example, reacted with thionyl chloride in the presence of triethylamine and N,N-dimethylformamide in acetonitrile at about

ambient temperature to form the corresponding imidazoyl chloride, which is reacted in situ with triethylamine, sodium azide and tetrabutylammonium bromide at 10-30°C to give the formula XIV compound.

Whereafter, an N-oxide or a non-toxic salt or an optically active form of a compound of the formula I may be obtained as described above if desired.

Certain of the intermediates defined herein are novel, for example the compounds of the formula IIIa, IIIb, IIIc, IVa, IVb, IVc, VIIIa, VIIIb, VIIIc and XIII and are provided as further independent features of the invention.

As stated above, the compounds of formula I will have beneficial pharmacological effects in warm-blooded animals (including man) in diseases and medical conditions where amelioration of the vasoconstrittor and fluid retaining properties of the renin-angiotensin-aldosterone system is desirable, at least in part by antagonism of one or more of the physiological actions of AII. The compounds of the invention will thus be useful in the treatment of diseases or medical conditions such as hypertension, congestive heart failure and/or hyperaldosteronism in warm-blooded animals (including man), as well as in other diseases or medical conditions in which the renin-angiotensin-aldosterone system plays a significant causative role. The compounds of the invention may also be useful for the treatment of ocular hypertension, glaucoma, cognitive disorders (such as Alzheimer's disease, amnesia, senile dementia and learning disorders), as well as other diseases such as renal failure, cardiac insufficiency, post-myocardial infarction, cerebrovascular disorders, anxiety, depression and certain mental illnesses such as schizophrenia.

The antagonism of one or more of the physiological actions of AII and, in particular, the antagonism of the interaction of AII with the receptors which mediate its effects on a target tissue, may be assessed using one or more of the following, routine laboratory

procedures:

Test A: This in vitro procedure involves the incubation of the test compound initially at a concentration of 100 micromolar (or less) in a buffered mixture containing fixed concentrations of radiolabelled AII and a cell surface membrane fraction prepared from a suitable angiotensin target tissue. In this test, the source of cell surface membranes is the guinea pig adrenal gland which is well known to respond to AII. Interaction of the radiolabelled AII with its receptors (assessed as radiolabel bound to the particulate membrane fraction following removal of unbound radiolabel by a rapid filtration procedure such as is standard in such studies) is antagonized by compounds which also bind to the membrane receptor sites and the degree of antagonism (observed in the test as displacement of membrane-bound radioactivity) is determined readily by comparing the receptor-bound radioactivity in the presence of the test compound at the specified test concentration with a control value determined in the absence of the test compound. Using this procedure compounds showing at least 50% displacement of radiolabelled AII binding at a concentration of 10^{-4} M are retested at lower concentrations to determine their potency. For determination of the IC_{50} (concentration for 50% displacement of radiolabelled AII binding), concentrations of the test compound are ordinarily chosen to allow testing over at least four orders of magnitude centred about the predicted approximate IC_{50}, which latter is subsequently determined from a plot of percentage displacement against concentration of the test compound.

In general, acidic compounds of formula I as defined above show significant inhibition in Test A at a concentration of about 50 micromolar or much less.

Test B: This in vitro test involves the measurement of the antagonistic effects of the test compound against AII-induced contractions of isolated rabbit aorta, maintained in a physiological salt solution at 37°C. In order to ensure that the effect of the compound is specific to antagonism of AII, the effect of the test compound on noradrenaline-induced contractions may also be determined in the same preparation.

In general, acidic compounds of formula I as defined above show significant inhibition in Test B at a final concentration of about 50 micromolar or much less. [Note: Compounds of formula I wherein Za, Zb or Zc is an ester group in general show only weak activity in the in vitro Tests A or B.]

Test C: This in vivo test involves using terminally-anaesthetised or conscious rats in which an arterial catheter has been implanted under anaesthesia for the measurement of changes in blood pressure. The AII antagonistic effects of the test compound following oral or parenteral administration, are assessed against angiotensin II-induced pressor responses. To ensure that the effect is specific, the effect of the test compound on vasopressin-induced pressor responses may also be determined in the same preparation.

The compounds of formula I generally show specific AII-antagonist properties in Test C at a dose of about 50 mg/kg body weight or much less, without any overt toxicological or other untoward pharmacological effect.

Test D: This in vivo test involves the stimulation of endogenous AII biosynthesis in a variety of species including rat, marmoset and dog by introducing a diet of low sodium content and giving appropriate daily doses of a saluretic known as frusemide. The test compound is then administered orally or parenterally to the animal in which an arterial catheter has been implanted under anaesthesia for the measurement of changes in blood pressure.

In general compounds of formula I will show AII-antagonist properties in Test D as demonstrated by a significant reduction in blood pressure at a dose of about 50 mg/kg body weight or much less, without any overt toxicological or other untoward pharmacological effect.

By way of illustration of the angiotensin II inhibitory properties of compounds of the formula I, the compound of Example 2 gave the following results in tests A and C described above:-
In test A: an IC_{50} of 1.51×10^{-8}M;
In test C: ED_{50} of 0.45 mg/kg (i.v. administration).

The compounds of formula I will generally be administered for therapeutic or prophylactic purposes to warm-blooded animals (including man) requiring such treatment in the form of a pharmaceutical composition, as is well known in the pharmaceutical art. According to a further feature of the invention there is provided a pharmaceutical composition comprising a compound of formula I, or a salt or N-oxide thereof as defined above, together with a pharmaceutically acceptable diluent or carrier. Such compositions will conveniently be in a form suitable for oral administration (e.g. as a tablet, capsule, solution, suspension or emulsion) or parenteral administration (e.g. as an injectable aqueous or oily solution, or injectable emulsion).

The compounds of formula I may also be advantageously administered for therapeutic or prophylactic purposes together with another pharmacological agent known in the general art to be of value in treating one or more of the diseases or medical conditions referred to hereinabove, such as a beta-adrenergic blocker (for example atenolol), a calcium channel blocker (for example nifedipine), an angiotensin converting enzyme (ACE) inhibitor (for example lisinopril) or a diuretic (for example furosemide or hydrochlorothiazide). It is to be understood that such combination therapy constitutes a further aspect of the present invention.

In general a compound of formula I (or a pharmaceutically acceptable salt thereof as appropriate) will generally be administered to man so that, for example, a daily oral dose of up to 50 mg/kg body weight (and preferably of up to 10 mg/kg) or a daily parenteral dose of up to 5 mg/kg body weight (and preferably of up to 1 mg/kg) is received, given in divided doses as necessary, the precise amount of compound (or salt) administered and the route and form of administration depending on size, age and sex of the person being treated and on the particular disease or medical condition being treated according to principles well known in the medical arts.

In addition to their aforesaid use in therapeutic medicine in humans, the compounds of formula I are also useful in the veterinary treatment of similar conditions affecting commercially valuable warm-blooded animals, such as dogs, cats, horses and cattle.

In general for such treatment, the compounds of the formula I will generally be administered in an analogous amount and manner to those described above for administration to humans. The compounds of formula I are also of value as pharmacological tools in the development and standardisation of test systems for the evaluation of the effects of AII in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the continuing search for new and improved therapeutic agents.

The invention will now be illustrated by the following non-limiting Examples in which, unless otherwise stated:-

(i) concentrations and evaporations were carried out by rotary evaporation in vacuo;

(ii) operations were carried out at room temperature, that is in the range 18-26°C;

(iii) flash column chromatography was performed on Merck Kieselgel 60 (Art. no. 9385) obtained from E Merck, Darmstadt, Germany;

(iv) yields, where given, are intended for the assistance of the reader only and are not necessarily the maximum attainable by diligent process development;

(v) ^{1}H NMR spectra were normally determined at 200 MHz in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard, and are expressed as chemical shifts (delta values) in parts per million relative to TMS using conventional abbreviations for designation of major peaks: s, singlet; m, multiplet; t, triplet; br, broad; d,doublet;

(vi) ^{13}C NMR spectra were normally determined at 100 MHz in $CDCl_3$ or d_6-dimethylsulphoxide (d_6-DMSO) using the solvent signal as internal standard, and are expressed as chemical shifts (delta values) in parts per million relative to TMS;

(vii) the purity of chemical products was assessed by nuclear magnetic resonance spectroscopy, thin layer chromatographic analysis and/or microanalysis: and

(viii) the term "1H-tetrazol-5-yl" stands for "1H-1,2,3,4-tetrazol-5-yl".

Example 1

Concentrated hydrochloric acid (0.5 ml) was added to a suspension of 4,6-dimethyl-3-phenyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1H-pyrazolo[4,3-c]pyridine (A) (500 mg) in methanol (5 ml) and the mixture was stirred for 30 minutes. Volatile material was removed by evaporation and the residue was washed with ether (4 x 4ml). The insoluble solid was recrystallised from a mixture of ethyl acetate/isopropanol (1:1 v/v) to give 4,6-dimethyl-3-phenyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)-methyl]-1H-pyrazolo[4,3-c]pyridine hydrochloride (260 mg), as a pink solid, m.p. 271-273°C; NMR (d_6-DMSO): 2.76(s, 3H), 2.79(s, 3H), 5,79(s, 2H), 7.09(d, 2H), 7.30(d, 2H), 7.48-7.68(complex m, 9H), 8.15(s, 1H); mass spectrum (positive fast atom bombardment (+ve FAB), $CHCl_3$, DMSO, CH_3OH, nitrobenzyl alcohol): 458 $(M+H)^+$; microanalysis, found: C,67.4; H,5.0; N,19.3%; $C_{28}H_{23}N_7.HCl.0.1C_3H_7OH$ requires: C,67.9; H,4.96; N,19.6%.

The starting material (A) was obtained as follows:-

(i) 3-benzoyl-1,4-dihydro-2,6-dimethyl-4-oxopyridine (1.0 g) (obtained as described in Monatshefte für Chemie, 1969, 100, 132) was added to phosphorus oxychloride (30 ml) and the mixture was heated at reflux for 3 hours. The mixture was cooled to ambient temperature and volatile material was removed by evaporation. The residue was added to crushed ice (50 g) and the mixture was basified with 4M sodium hydroxide solution. The mixture was then extracted with dichloromethane (4 x 25 ml) and the combined extracts were dried ($MgSO_4$). Solvent was removed by evaporation to give 3-benzoyl-4-chloro-2,6-dimethylpyridine (B) (1.05 g), as a pale brown solid; NMR ($CDCl_3$): 2.56(s, 3H), 2.78(s, 3H), 7.32(s, 1H), 7.51-7.78(complex m, 5H); mass spectrum (chemical ionisation (CI), ammonia): 246 /248 $(M+H)^+$.

(ii) Hydrazine hydrate (0.94 g) was added to a solution of compound B (0.92 g) in ethanol (5 ml) and the mixture was heated at reflux for 48 hours. The mixture was cooled to ambient temperature and volatile material was removed by evaporation. The residue was dissolved in ethyl acetate and the solution was washed with saturated sodium bicarbonate solution and dried ($MgSO_4$). Solvent was removed by

evaporation and the residue was purified by flash chromatography, eluting with ethyl acetate/hexane (4:1 v/v), to give 4,6-dimethyl-1H-pyrazolo[4,3-c]pyridine (C) (0.60 g), as a white solid, m.p. 225-227°C; NMR ($CDCl_3$); 2.55(s, 3H), 2.60(s, 3H), 7.08(s, 1H), 7.44-7.59(m, 5H), 12.68(s, 1H); mass spectrum (CI, ammonia): $224(M+H)^+$.

(iii) Sodium hydride (60% dispersion in mineral oil, 80 mg) was added to a stirred solution of compound C (0.4 g) in DMF (30 ml) and the mixture stirred at room temperature for 40 minutes. 5-[2-(4'-bromomethylbiphenylyl)]-2-triphenylmethyl-2H-tetrazole (1.39 g) (obtained as described in European patent application no. 0291969) was added and the mixture was stirred at ambient temperature for 16 hours. The mixture was partitioned between ethyl acetate (100 ml) and water (100 ml) and the organic layer was separated and dried ($MgSO_4$). Solvent was removed by evaporation and the residue was purified by flash chromatography, eluting with ethyl acetate/hexane (9:11 v/v), to give 4,6-dimethyl-3-phenyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1H-pyrazolo[4,3-c]pyridine (A) (0.99 g) as a white foam; NMR ($CDCl_3$): 2.54(s, 3H), 2.58(s, 3H), 5.44(s, 2H), 6.87-7.5(complex m, 28H), 7.92(m, 1H); mass spectrum (+ve FAB, DMSO/nitrobenzyl alcohol): $700(M+H)^+$.

Example 2

Using an analogous procedure to that described in Example 1, but starting from 6-ethyl-4-methyl-3-phenyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1H-pyrazolo[4,3-c]pyridine (A) and crystallising the product from ethanol/ether (1:1 v/v), there was thus obtained 6-ethyl-4-methyl-3-phenyl-1-[(2'-(1H-tetrazol-5-yl)-biphenyl-4-yl)methyl]-1H-pyrazolo[4,3-c]pyridine hydrochloride (37% yield), as a solid, m.p. 262.5-264°C; NMR (d_6-DMSO): 1.39(t, 3H), 2.80(s, 3H), 3.1(q, 2H), 5.03(s, 2H), 7.1(d, 2H), 7.3(d, 2H), 7.48-7.72(complex m, 9H), 8.17(s, 1H); mass spectrum (+ve FAB, DMSO/nitrobenzyl alcohol): $472(M+H)^+$; microanalysis, found: C,67.7; H5.3; N19.1%; $C_{29}H_{25}N_7.HCl.0.1C_2H_5OH.0.57H_2O$ requires: C,68.3; H,5.2; N,19.1%

The starting material A was obtained as follows:-

(i) A mixture of 3-amino-1-phenyl-2-buten-1-one (2.3 g) and 5-(1-hydroxypropylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.0 g) was heated at 120°C for 1 hour. The mixture was cooled to ambient temperature and the residue was purified by flash chromatography, eluting with dichloromethane/methanol (19:1 v/v), to give 3-benzoyl-1,4-dihydro-6-ethyl-2-methyl-4-oxopyridine (B) (0.95 g), as a solid, m.p. 203°C; NMR (d_6-DMSO): 1.2(t, 3H), 2.07(s, 3H), 2,5(q, 2H), 5.96(s, 1H), 7.44-7.50(m, 2H), 7.57-7.60(m, 1H), 7.72-7.86(m, 2H), 11.3(broad s, 1H); mass spectrum (chemical ionisation, ammonia): 242$(M+H)^+$.

(ii) Using an analogous procedure to that described in Example 1, part (i), but starting from compound B there was obtained 3-benzoyl-4-chloro-6-ethyl-2-methylpyridine (C) (in 78% yield) as an oil; NMR (d_6-DMSO): 1.27(t, 3H), 2.26(s, 3H), 2.79(q, 2H), 7.44(s, 1H), 7.58-7.62(m, 2H), 7.74(m, 3H); mass spectrum (chemical ionisation, ammonia): 260/262$(M+H)^+$.

(iii) Using an analogous procedure to that described in Example 1, part (ii), but starting from compound C there was obtained 4-methyl-6-ethyl-1H-pyrazolo[4,3-c]pyridine (D) (in 85% yield) as an oil; NMR ($CDCl_3$): 1.33(t, 3H) 2.6(s, 3H), 2.85(q, 2H), 7.12(s, 1H), 7.40-7.60(m, 5H) ; mass spectrum (chemical ionisation, ammonia): 238$(M+H)^+$.

(iv) Using an analogous procedure to that described in Example 1, part (iii), but starting from compound D there was obtained 6-ethyl-4-methyl-3-phenyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1H-pyrazolo[4,3-c]pyridine (A) (in 36% yield), as a solid; NMR (d_6-DMSO): 1.3(t, 3H), 2.6(s, 3H), 2.85(q, 2H), 5.48(s, 2H), 6.07-7.58(complex m, 29H); mass spectrum (+ve FAB, DMSO/nitrobenzyl alcohol): 714$(M+H)^+$.

Example 3

(Note: all parts by weight)

The compounds of the invention may be administered for therapeutic or prophylactic use to warm-blooded animals such as man in the form of conventional pharmaceutical compositions, typical examples of which include the following:-

a) **Capsule** (for oral administration)

Active ingredient *	20
Lactose powder	578.5
Magnesium stearate	1.5

b) **Tablet** (for oral administration)

Active ingredient *	50
Microcrystalline cellulose	400
Starch (pregelatinised)	47.5
Magnesium stearate	2.5

c) **Injectable Solution** (for intravenous administration)

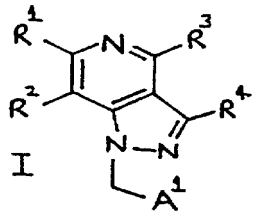
Active ingredient *	0.05 - 1.0
Propylene glycol	5.0
Polyethylene glycol (300)	3.0 - 5.0
Purified water	to 100%

d) **Injectable Suspension** (for intramuscular administration)

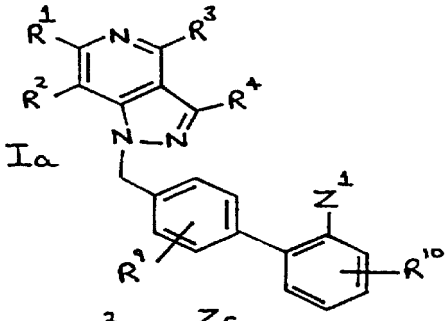
Active ingredient *	0.05 - 1.0
Methylcellulose	0.5
Tween 80	0.05
Benzyl alcohol	0.9
Benzalkonium chloride	0.1
Purified water	to 100%

Note: the active ingredient * may typically be an Example described hereinbefore and will conveniently be present as a pharmaceutically acceptable acid-addition salt, such as the hydrochloride salt. Tablets and capsules formulations may be coated in conventional manner in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating.

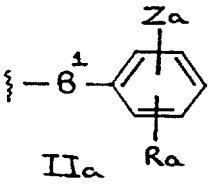
Chemical Formulae



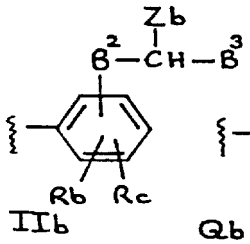
I



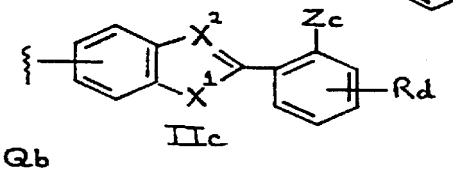
Ia



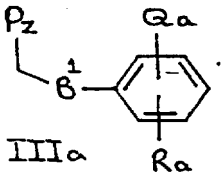
IIa



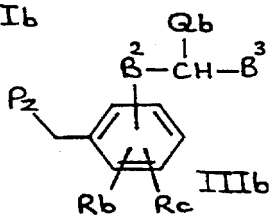
IIb



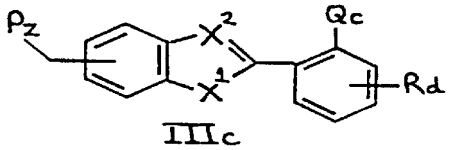
IIc



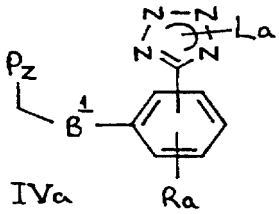
IIIa



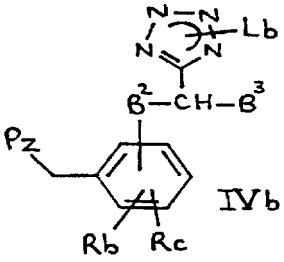
IIIb



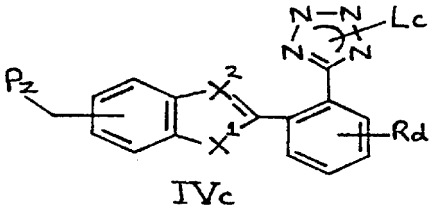
IIIc



IVa

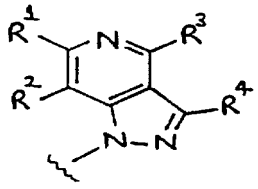


IVb

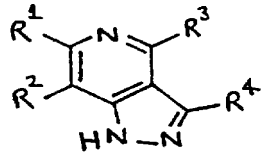


IVc

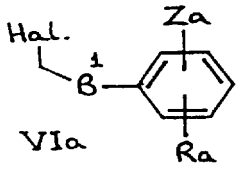
Note: Pz =



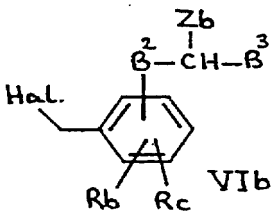
Chemical Formulae
(continued)



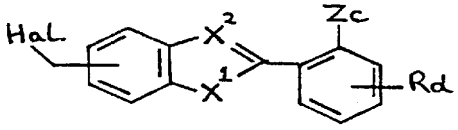
V



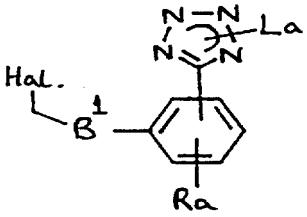
VIa



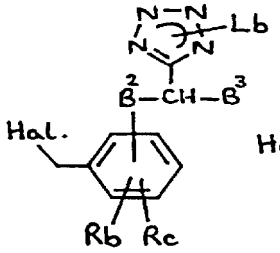
VIb



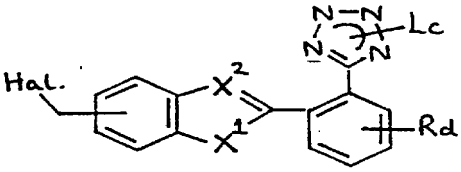
VIc



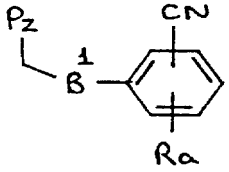
VIIa



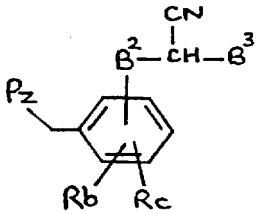
VIIb



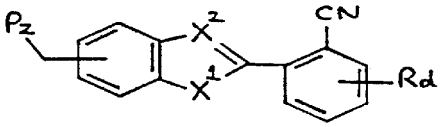
VIIc



VIIIa

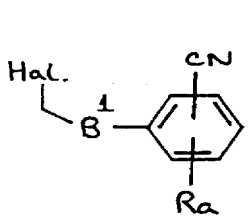


VIIIb

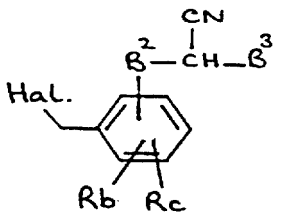


VIIIc

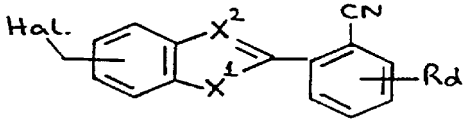
Chemical Formulae
(continued)



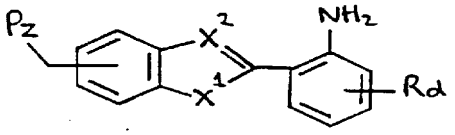
IXa



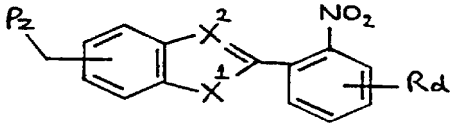
IXb



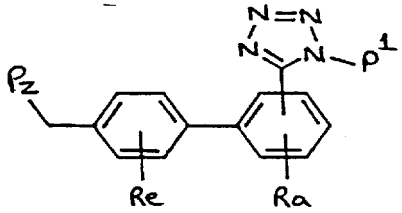
IXc



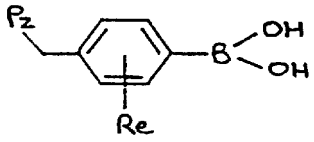
X



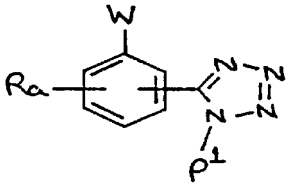
XI



XII

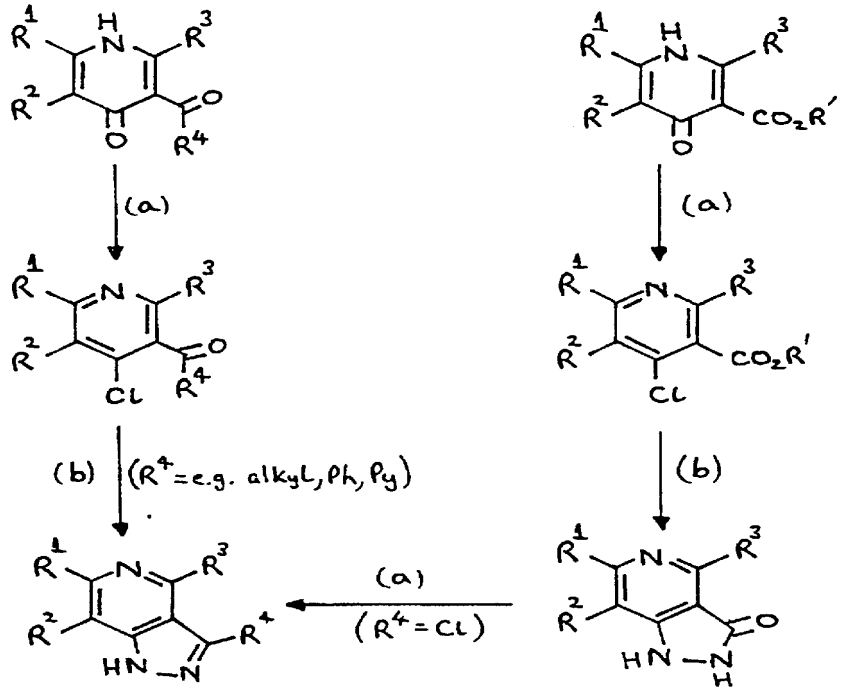


XIII



XIV

Scheme 1



Note: R' = lower alkyl; Ph = phenyl; Py = pyridyl

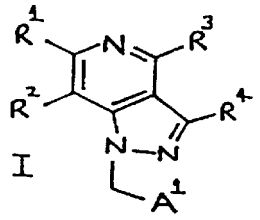
Reagents: (a) $POCl_3$, reflux

(b) hydrazine hydrate, ethanol, reflux

CLAIMS

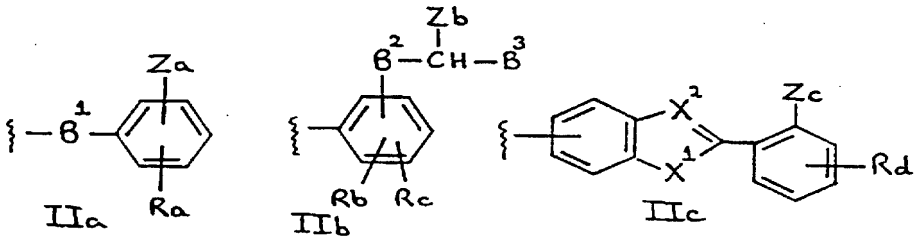
What we claim is:-

1. A pyrazolopyridine derivative of the formula I



I

wherein
R^1 is hydrogen, (1-8C)alkyl, (3-8C)cycloalkyl, phenyl or substituted (1-4C)alkyl, the latter containing one or more fluoro substituents or bearing a (3-8C)cycloalkyl, (1-4C)alkoxy or phenyl substituent;
R^2 is hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, carboxy, (1-4C)alkoxycarbonyl, (3-6C)alkenyloxycarbonyl, cyano, nitro, carbamoyl, (1-4C)alkanoyl, N-alkylcarbamoyl and di-(N-alkyl)carbamoyl of up to 7 carbon atoms, amino, alkylamino and dialkylamino of up to 6 carbon atoms, 3-(1-4C)alkylureido and (1-4C)alkanoylamino;
R^3 is selected from halogeno, (1-4C)alkoxy, hydroxy, amino, alkylamino and dialkylamino of up to 6 carbon atoms, and any of the values defined for R^1;
R^4 is selected from (1-4C)alkoxy, halogeno, hydroxy(1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, (3-6C)alkenyloxycarbonyl, cyano, nitro, carbamoyl, N-alkylcarbamoyl and di-(N-alkyl)carbamoyl of up to 7 carbon atoms, (1-4C)alkanoyl, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl, pyridyl and any of the values defined for R^1;
A^1 is a group of the partial formula IIa, IIb or IIc



wherein

(1) in partial formula IIa, B^1 is a direct bond or is phenylene optionally bearing a substituent selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, (1-4C)alkanoyl, trifluoromethyl, cyano and nitro; Ra is hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano, trifluoromethyl or nitro; and Za is 1H-tetrazol-5-yl, a carboxy group or in vivo hydrolysable ester thereof, -CO.NH.(1H-tetrazol-5-yl), or a group of the formula $-CO.NH.CO_2R^8$ in which R^8 is (1-6C)alkyl, (3-8C)cycloalkyl, trifluoromethyl or phenyl;

(2) in partial formula IIb, B^2 is oxygen, sulphur or a group of the formula $-NR^5-$ in which R^5 is hydrogen or (1-4C)alkyl; Zb has any of the values defined above for Za; B^3 is phenyl optionally bearing one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy and halogeno; and Rb and Rc are independently selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy and halogeno; and

(3) in partial formula IIc, Zc is 1H-tetrazol-5-yl, carboxy or in vivo hydrolysable ester thereof or a group of the formula CF_3SO_2NH-; Rd is selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, cyano and nitro; X^1 is oxygen, sulphur or a group of the formula $-NR^6-$ in which R^6 is hydrogen or (1-4C)alkyl; and X^2 is nitrogen or is a group of the formula $-C(R^7)=$ wherein R^7 is hydrogen, (1-4C)alkyl optionally containing one or more fluoro substituents, carbamoyl or N-alkyl or di-(N-alkyl)carbamoyl of up to 7 carbon atoms, halogeno, cyano, (1-4C)alkoxycarbonyl or (1-4C)alkanoyl;

and wherein any of said phenyl moieties may be unsubstituted or bear one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano and trifluoromethyl; or an N-oxide

thereof; or a non-toxic salt thereof.

2. A compound as claimed in claim 1 wherein
R^1 is hydrogen, methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl, hexyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-methoxyethyl, 2-ethoxyethyl, benzyl, 1-phenylethyl and 2-phenylethyl;
R^2 is hydrogen, methyl, ethyl, propyl, methoxy, ethoxy, fluoro, chloro, bromo, iodo, trifluoromethyl, carboxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, allyloxycarbonyl, 2-methyl-2-propenyloxycarbonyl, 3-methyl-3-butenyloxycarbonyl, cyano, nitro, carbamoyl, formyl, acetyl, propionyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, amino, methylamino, ethylamino, butylamino, dimethylamino, diethylamino, dipropylamino, formamido, acetamido, propanamido, 3-methylureido, 3-ethylureido or 3-propylureido;
R^3 is selected from hydrogen, methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl, hexyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-methoxyethyl, 2-ethoxyethyl, benzyl, 1-phenylethyl, 2-phenylethyl, fluoro, chloro, bromo, iodo, methoxy, ethoxy, hydroxy, amino, methylamino, ethylamino, butylamino, dimethylamino, diethylamino and dipropylamino;
R^4 is selected from hydrogen, methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl, hexyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-methoxyethyl, 2-ethoxyethyl, benzyl, 1-phenylethyl, 2-phenylethyl, fluoro, chloro, bromo, iodo, methoxy, ethoxy, hydroxymethyl, 1-hydorxyethyl, 2-hydroxyethyl, carboxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, allyloxycarbonyl, 2-methyl-2-propenyloxycarbonyl, 3-methyl-3-butenyloxycarbonyl, cyano, nitro, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, formyl, acetyl,

propionyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl, ethylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl and pyridyl;

A^1 is a group of partial formula IIa, IIb or IIc wherein

(1) in partial formula IIa, B^1 is a direct bond or is phenylene optionally bearing a substituent selected from methyl, ethyl, methoxy, ethoxy, fluoro, chloro, bromo, formyl, acetyl, propionyl, trifluoromethyl, cyano and nitro; Ra is hydrogen, methyl, ethyl, methoxy, ethoxy, fluoro, chloro, bromo, cyano, trifluoromethyl or nitro; Za is 1H-tetrazol-5-yl, carboxy, a carboxylic ester derived from a (1-6C)alkanol, phenol or glycerol, -CO.NH.(1H-tetrazol-5-yl) or a group of the formula $-CO.NH.CO_2R^8$ in which R^8 is methyl, ethyl, propyl, isopropyl, butyl, pentyl, cyclobutyl, cyclopentyl, cyclohexyl, trofluoromethyl or phenyl;

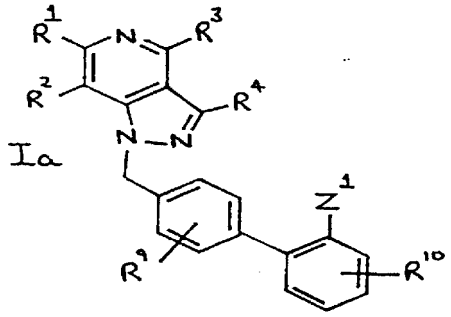
(2) in partial formula IIb, B^2 is oxygen, sulphur or a group of the formula $-NR^5-$ in which R^5 is hydrogen, methyl, ethyl or propyl; Zb is 1H-tetrazol-5-yl, carboxy, a carboxylic ester derived from a (1-6C)alkanol, phenol or glycerol, -CO.NH.(1H-tetrazol-5-yl) or a group of the formula $-CO.NH.CO_2R^8$ in which R^8 is methyl, ethyl, propyl, isopropyl, butyl, pentyl, cyclobutyl, cyclopentyl, cyclohexyl, trofluoromethyl or phenyl; B^3 is phenyl optionally bearing one or two substituents independently selected from methyl, ethyl, methoxy, ethoxy, fluoro, chloro and bromo; and Rb and Rc are independently selected from hydrogen, methyl, ethyl, methoxy, ethoxy, fluoro, chloro and bromo; and

(3) in partial formula IIc, Zc is 1H-tetrazol-5-yl, carboxy, a carboxylic ester derived from a (1-6C)alkanol, phenol or glycerol, or a group of the formula CF_3SO_2NH-; Rd is selected from hydrogen, methyl, ethyl, methoxy, ethoxy, fluoro, chloro, bromo, trifluoromethyl, cyano and nitro; X^1 is oxygen, sulphur or a group of the formula $-NR^6-$ in which R^6 is hydrogen, methyl, ethyl or propyl; and X^2 is nitrogen or is a group of the formula $-C(R^7)-$ wherein R^7 is hydrogen, methyl, ethyl, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, fluoro, chloro, bromo, iodo, cyano, methoxycarbonyl, ethoxycarbonyl, formyl, acetyl or propionyl;

and wherein any of said phenyl moieties may be unsubstituted or bear one or two substituents independently selected from methyl, ethyl, methoxy, ethoxy, fluoro, chloro, bromo, cyano and trifluoromethyl; or an N-oxide thereof; or a non-toxic salt thereof.

3. A compound as claimed in claim 1 or 2 wherein A^1 is a group of partial formula IIa.

4. A compound of the formula Ia



Ia

wherein R^1, R^2, R^3 and R^4 have any of the meanings defined in any one of claims 1 to 3; R^9 and R^{10} are independently selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, cyano and nitro; and Z^1 is 1H-tetrazol-5-yl or carboxy; and the non-toxic salts thereof.

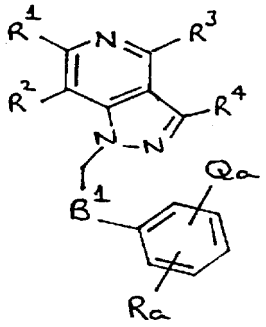
5. A compound as claimed in claim 4 wherein R^1 is (1-4C)alkyl; R^2, R^9 and R^{10} are all hydrogen; R^3 is (1-4C)alkyl; R^4 is phenyl optionally bearing a halogeno, (1-4C)alkoxy or (1-4C)alkyl substituent; and the non-toxic salts thereof.

6. A compound of the formula I selected from:
4,6-dimethyl-3-phenyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)-methyl]-1H-pyrazolo[4,3-c]pyridine; and
6-ethyl-4-methyl-3-phenyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)-methyl]-1H-pyrazolo[4,3-c]pyridine; or a non-toxic salt thereof.

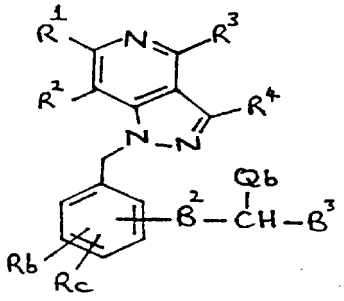
7. A salt as claimed in any one preceding claim which is selected from salts with acids forming physiologically acceptable anions and, for those compounds of the formula I which are acidic, alkali metal, alkaline earth metal, aluminium and ammonium salts, and salts with organic bases affording physiologically acceptable cations.

8. A process for the manufacture of a compound of formula I or a non-toxic salt thereof, as claimed in claim 1, which is characterised in that:-

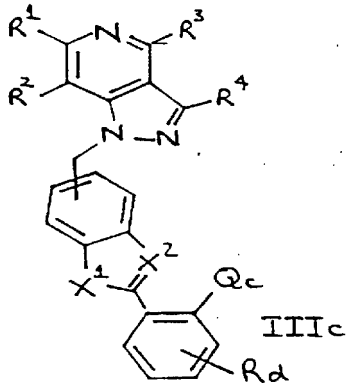
(a) For those compounds of formula I in which A^1 is a group of partial formula IIa, IIb or IIc in which Za, Zb and Zc respectively are carboxy, a carboxylic acid derivative of the formula IIIa, IIIb or IIIc



IIIa



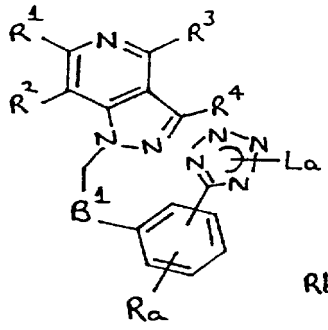
IIIb



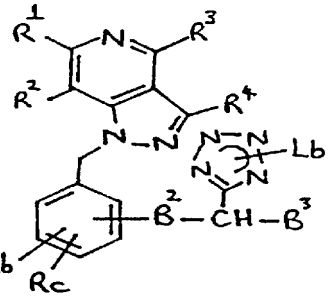
IIIc

in which Qa, Qb and Qc respectively are protected carboxy groups selected from (1-6C)alkoxycarbonyl, phenoxycarbonyl, benzyloxycarbonyl and carbamoyl, is converted to carboxy;

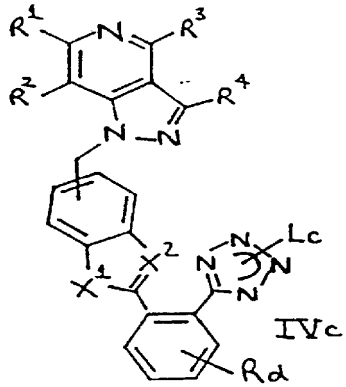
(b) For those compounds of formula I in which A^1 is a group of partial formula IIa, IIb or IIc in which Za, Zb and Zc respectively are tetrazolyl, a compound of the formula IVa, IVb or IVc



IVa



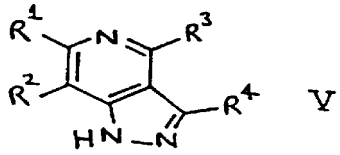
IVb



IVc

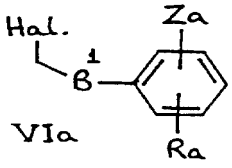
in which La, Lb and Lc respectively are suitable protecting groups affixed to a nitrogen of the tetrazolyl moiety, is deprotected;

(c) A compound of the formula V

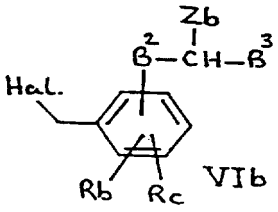


V

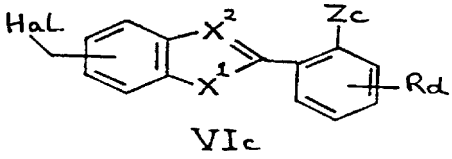
is alkylated with a compound of the formula VIa, VIb or VIc



VIa



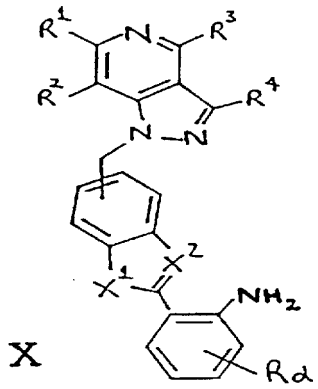
VIb



VIc

wherein Hal. stands for a suitable leaving group;

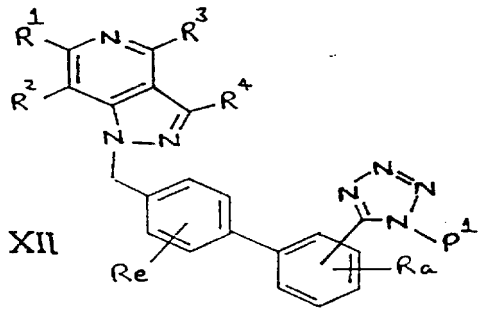
(d) For those compounds of the formula I wherein A^1 is a group of partial structure IIc in which Zc is a group of the formula CF_3SO_2NH-, a compound of the formula X



X

is reacted with trifluorosulphonic acid anhydride; or

(e) For a compound of the formula I wherein A^1 is a group of the partial structure IIa in which Za is tetrazolyl and B^1 is p-phenylene optionally bearing a substituent selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, (1-4C)alkanoyl, trifluoromethyl, cyano and nitro, a compound of the formula XII



XII

wherein P^1 is an electron-deficient phenyl group; Re is hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, (1-4C)alkanoyl, trifluoromethyl, cyano and nitro, is reacted with a base selected from an alkali metal hydroxide, (1-12C)alkanolate, (1-12C)alkanethiolate, phenolate, thiophenolate or diphenylphosphide, wherein any phenyl ring of the latter three groups may optionally bear a (1-4C)alkyl, (1-4C)alkoxy or halogeno group;

whereafter: when a compound of the formula I is required wherein Za, Zb or Zc is 1H-tetrazol-5-yl, a compound of the formula I wherein Za, Zb or Zc is a carboxylic acid or ester group respectively is converted into the corresponding nitrile under standard conditions, followed by reaction of the nitrile with an azide;

when a compound of the formula I is required wherein Za, Zb or Zc is -CO.NH.(1H-tetrazol-5-yl), a group of the formula $-CO.NH.SO_2R^8$ or an ester group, a corresponding carboxylic acid of the formula I in which Za, Zb or Zc is carboxy (or a reactive derivative of said acid) is reacted with 5-aminotetrazole, a sulphonamide of the formula $NH_2.SO_2R^8$ or an appropriate alcohol, or with a salt thereof;

when an N-oxide of a compound of the formula I is required, a compound of the formula I is oxidised;

when a non-toxic salt of a compound of formula I is required, it is obtained by reaction with the appropriate acid or base affording a physiologically acceptable ion, or by any other conventional salt formation procedure; and

when an optically active form of a compound of formula I is required, one of the aforesaid processes (a)-(e) is carried out using an optically active starting material, or the racemic form of a compound of formula I in which Za, Zb or Zc is an acidic group is resolved by reaction with an optically active form of a suitable organic base followed by conventional separation of the diastereoisomeric mixture of salts thus obtained, and liberation of the required optically active form of said compound of formula I by conventional treatment with acid;

and wherein R^1, R^2, R^3, R^4 and A^1 have any of the meanings defined in any of claims 1 to 5 unless otherwise stated.

9. A pharmaceutical composition which comprises a compound of the formula I or Ia, or a non-toxic salt thereof, as claimed in any of claims 1 to 7, together with a pharmaceutically acceptable diluent or carrier.

10. A compound of the formula IVa wherein R^1, R^2, R^3, R^4, B^1 and Ra have any of the meanings defined in any of claims 1 to 5, and La is a protecting group.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 93/01635

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D471/04 A61K31/435 //(C07D471/04,231:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 399 731 (ICI) 28 November 1990 cited in the application see claims 1,11	1,9
A	EP,A,0 497 516 (MERCK) 5 August 1992 cited in the application see claims 1,8	1,9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 November 1993	23. 11. 93

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	ALFARO FAUS, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/GB 93/01635

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0399731	28-11-90	AU-B-	621483	12-03-92
		AU-A-	5477990	29-11-90
		JP-A-	3005480	11-01-91
EP-A-0497516	05-08-92	US-A-	5124335	23-06-92
		CA-A-	2060055	31-07-92
		JP-A-	5001062	08-01-93